

AWARD NUMBER: W81XWH-14-2-0137

TITLE: Blood Biomarker Profile of TBI-Associated Cognitive Impairment Among Old and Young Veterans

PRINCIPAL INVESTIGATOR: Kristine Yaffe, MD

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education  
San Francisco, CA 94121

REPORT DATE: October 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;  
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

# REPORT DOCUMENTATION PAGE

Form Approved  
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

<b>1. REPORT DATE</b> October 2015		<b>2. REPORT TYPE</b> Annual		<b>3. DATES COVERED</b> 30 Sep 2014 - 29 Sep 2015	
<b>4. TITLE AND SUBTITLE</b>  Blood Biomarker Profile of TBI-Associated Cognitive Impairment Among Old and Young Veterans				<b>5a. CONTRACT NUMBER</b>	
				<b>5b. GRANT NUMBER</b> W81XWH-14-2-0137	
				<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b>  Kristine Yaffe, MD email: kristine.yaffe@ucsf.edu				<b>5d. PROJECT NUMBER</b>	
				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b> Northern California Institute for Research and Education 4150 Clement Street (151 NC) San Francisco, CA 94121-1545  Henry Jackson Foundation for the Advancement of Military Medicine 6720A Rockledge Drive, Suite 100 Bethesda, MD 20817-1805				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b>  U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
				<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b> Approved for Public Release; Distribution Unlimited					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> The goal of this project is to define the biomarker profile of TBI-associated CI in veterans and compare it to that of veterans with AD and to age-matched controls. Our overall hypothesis is that TBI-associated CI involves a unique biomarker profile that has features distinguishable from AD and normal aging. Specifically, we hypothesize that: 1) patients with TBI associated CI will have higher phospho-tau/total tau ratio than controls who have not had a TBI, and that 2) TBI-associated CI will be associated with elevations in inflammatory markers compared to controls and 3) a decrease in b-amyloid measures compared to controls but not as low as in the setting of AD. We currently have data collection ongoing at both sites. As of 30-SEP-2015, data from 31 participants with TBI and 30 controls has been collected. Once data collection is complete, we will examine the biomarker profile of the groups. This study will refine our understanding of the underlying mechanisms in TBI-associated CI, help predict who is at greatest risk of developing CI in veterans with TBI, and identify who may benefit from interventions and treatment for CI and its prevention.					
<b>15. SUBJECT TERMS</b> Traumatic brain injury (TBI), dementia, chronic traumatic encephalopathy (CTE), blood biomarkers, aging, cognitive impairment (CI), Alzheimer's Disease (AD)					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>  Unclassified	<b>18. NUMBER OF PAGES</b>  11	<b>19a. NAME OF RESPONSIBLE PERSON</b> USAMRMC
<b>a. REPORT</b> Unclassified	<b>b. ABSTRACT</b> Unclassified	<b>c. THIS PAGE</b> Unclassified			<b>19b. TELEPHONE NUMBER</b> (include area code)

## Table of Contents

	<u>Page</u>
Introduction -----	4
Key Words -----	4
Accomplishments -----	4
Impact -----	5
Changes/Problems -----	6
Products -----	6
Participants & Other Collaborating Organizations -----	7
Special Reporting Requirements -----	11

## Introduction

Military personnel are at high risk for traumatic brain injury (TBI). Two well-recognized and important adverse outcomes of TBI are cognitive impairment (CI) and dementia. While most studies report a 2-3 times increased risk of dementia associated with TBI, the underlying mechanism and type of dementia associated with TBI remains unclear. Some studies link TBI to Alzheimer disease (AD) while others suggest the TBI-associated dementia is more similar to chronic traumatic encephalopathy (CTE). The goal of this project is to define the biomarker profile of TBI-associated CI in veterans and compare it to that of veterans with AD and to age-matched controls. Our overall hypothesis is that TBI-associated CI involves a unique biomarker profile that has features distinguishable from AD and normal aging. Specifically, we hypothesize that: 1) patients with TBI associated CI will have higher phospho-tau/total tau ratio than controls who have not had a TBI, and that 2) TBI-associated CI will be associated with elevations in inflammatory markers compared to controls and 3) a decrease in b-amyloid measures compared to controls but not as low as in the setting of AD. This study will refine our understanding of the underlying mechanisms in TBI-associated CI, help predict who is at greatest risk of developing CI in veterans with TBI, and identify who may benefit from interventions and treatment for CI and its prevention.

## Key Words

Traumatic brain injury (TBI), dementia, chronic traumatic encephalopathy (CTE), blood biomarkers, aging, cognitive impairment (CI), Alzheimer 's disease (AD)

## Accomplishments

- **What were the major goals of the project?**
  - Planning, study design, and regulatory approval: Months 1-6
    - Study protocols were approved at both sites in the first quarter of the project. The study protocol, measurements and operations manual were completed in the first six months as planned.
  - Identify and enroll 80 older veterans with TBI and 80 normal controls at Armed Forces Retirement Home (AFRH), Washington, DC, and Veterans Home of California-Yountville (VHC-Y), Yountville, CA: Months 6-18
    - Data collection is currently ongoing at both sites.
  - Enroll 80 veterans with mild Alzheimer Disease (AD) at AFRH and VHC-Y: Months 18-30
    - We are currently determining the optimal methods for identifying and recruiting these participants at both sites.
  - Identify blood biomarker profile of TBI and compare to that of AD and controls: Months 24-36
    - Nothing to report

- **What was accomplished under these goals?**

In the first quarter of the project, we obtained first level UCSF CHR and second level HRPO approval for our study protocol. UCSF approval was obtained for protocol “Blood Biomarker Profile of TBI-Associated Cognitive Impairment among Old and Young Veterans” on 05-NOV-2014. This protocol was reviewed and approved by the US Army Medical Research and Material Command (USAMRMC), Office of Research Protection (ORP), and HRPO on 21-NOV-2014.

The sub-site Uniformed Services University of the Health Sciences (USUHS) submitted their protocol, “Blood Biomarker Profile of TBI-Associated Cognitive Impairment among Old and Young Veterans”, to the USUHS Institutional Review Board and received approval on 21-OCT-2014. This protocol was reviewed and approved by the US Army Medical Research and Material Command (USAMRMC), Office of Research Protection (ORP), and HRPO on 21-NOV-2014.

In the second quarter of the project we finalized the study protocol, measurements, and operations manual. Supplies for blood collection and storage were purchased. Data collection commenced at the Yountville site in JAN 2015. We had regular conference calls and e-mail contact with the sub-site USUHS regarding study initiation and progress.

In the third quarter of the project we continued data collection at the Yountville site, and the Armed Forces Retirement Home site finalized their site approvals.

The Armed Forces Retirement Home began data collection as of 1-JUL-2015. As of 30-SEP-2015, data has been collected on a total of 61 participants at both study sites: 31 veterans with a history of TBI and 30 veterans with no TBI history. Broken down by site, the VHC-Y site has 23 TBI and 22 Controls; the AFRH site has 8 TBI and 8 Controls.

- **What opportunities for training and professional development has the project provided?**
  - Nothing to report
- **How were the results disseminated to communities of interest?**
  - Nothing to report
- **What do you plan to do during the next reporting period to accomplish the goals?**
  - In the next reporting period we will continue data collection on participants with TBI and controls. We will begin recruiting and collecting data on participants with mild AD.

## **Impact**

- **What was the impact on the development of the principal discipline(s) of the project?**
  - Nothing to report
- **What was the impact on other disciplines?**

- Nothing to report
- **What was the impact on technology transfer?**
  - Nothing to report
- **What was the impact on society beyond science and technology?**
  - Nothing to report

## Changes/Problems

- **Changes in approach and reasons for change**
  - Nothing to report
- **Actual or anticipated problems or delays and actions or plans to resolve them**
  - The Armed Forces Retirement Home site required additional site approvals and data collection was delayed until July 2015. However, the site is now up and running.
- **Changes that had a significant impact on expenditures**
  - Although, we were awarded the grant on October 1, 2014, due to delays from first level UCSF CHR and second level HRPO approval, we were delayed in initiating spending. Per our institutional rules, we are required to have approvals in place before we can begin to spend or execute a subcontract. In the second quarter we received all levels of approval, and our institution set-up the award. We added all staff to the project. The subcontract with HJF was executed, and first invoices were submitted in the third quarter. Due to these delays, we may need to request a NCE to complete the project as originally designed.
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
  - Nothing to report

## Products

- **Publications, conference papers, and presentations**
  - **Journal publications.** Nothing to report
  - **Books or other non-periodical, one-time publications.** Nothing to report
  - **Other publications, conference papers, and presentations.** Nothing to report
- **Website(s) or other Internet site(s)**  
Nothing to report
- **Technologies or techniques**  
Nothing to report
- **Inventions, patent applications, and/or licenses**  
Nothing to report
- **Other Products**  
Nothing to report

## Participants and other collaborating organizations

- What individuals have worked on the project?

Name:	<i>Kristine Yaffe</i>
Project Role:	<i>Principal Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>KYAFFE</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Yaffe provides leadership and oversees research and data collection at both sites.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Ramon Diaz-Arrastia</i>
Project Role:	<i>Principal Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>RDIAZA</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Diaz-Arrastia provides leadership and oversees data collection at the AFRH site.</i>
Funding Support:	<i>Federal employee, salary contained through his appointment.</i>

Name:	<i>Joel Kramer</i>
Project Role:	<i>Co-Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>JKRAMER</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Kramer provides cognitive testing expertise and oversees the neuropsychological testing.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Kimbra Kenney</i>
Project Role:	<i>Co-Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>KKENNEY</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Kenney provides neurological expertise and oversees the data collection and neurological battery at the AFRH site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Carrie Peltz</i>
Project Role:	<i>Project Coordinator</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Dr. Peltz coordinates the project at both sites and monitors the day-to-day progress at the VHC-Y site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Kim Kelley</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>5</i>
Contribution to Project:	<i>Ms. Kelley collects data at the VHC-Y site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Dan Freimer</i>
Project Role:	<i>Research Associate</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Mr. Freimer assists with project coordination and data collection at the VHC-Y site.</i>
Funding Support:	<i>n/a</i>



Name:	<i>Erika Silverman</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	3
Contribution to Project:	<i>Ms. Silverman collects data at the AFRH site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Leah Harburg</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	3
Contribution to Project:	<i>Ms. Harburg collects data at the AFRH site.</i>
Funding Support:	<i>n/a</i>

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

**Dr. Yaffe:**

Summary: Dr. Yaffe had one grant begin and two grants end.

Title: Determinants of midlife & Longitudinal change in cognitive function: CARDIA study (Yaffe: Multiple-PI)

Time Commitment: 1.08 calendar months

Supporting Agency: NHLBI

Performance Period: 12/1/14-11/20/18

Level of Funding: \$658,155

Title: Endophenotypes of dementia after traumatic brain injury in retired military service members (Yaffe: PI)

Time Commitment: 1.8 calendar months

Supporting Agency: DoD, TATRC

Performance Period: 9/1/12-2/28/14

Level of Funding: \$480,000

Title: Glucose Regulation, Cognitive & Brain Changes in Elders (Yaffe: PI)  
Time Commitment: .36 calendar months  
Supporting Agency: American Health Assistance Foundation  
Performance Period: 4/1/10-3/31/14  
Level of Funding: \$394,755

**Dr. Diaz-Arrastia**

Summary: Dr. Diaz-Arrastia had one grant begin and one grant end.

Title: TBI Endpoints Development (TED) (Diaz-Arrastia Co-PI) (Manley PI)  
Time Commitment: 1.0 calendar month  
Supporting Agency: DoD/USAMRAA  
Performance Period: 09/01/2014-08/31/2016  
Level of Funding: 414,995

Title: Endophenotypes of dementia after traumatic brain injury in retired military service members  
(Diaz-Arrastia, Co-I)  
Time Commitment: 3 calendar months  
Supporting Agency: CDMRP, DoD  
Performance Period: 9/1/12-2/28/14  
Level of Funding: \$480,000

**Dr. Kenney:**

Summary: Dr. Kenney had three new grants begin and one end.

Title: Docosahexaenoic acid (DHA) therapy for traumatic brain injury: A biomarker driven approach  
Time Commitment: 4.0 calendar months  
Supporting Agency: CNRM, USUHS  
Level of Funding: \$1,000,000  
Performance Period: 2/1/2015 – 1/31/2017

Title: Cerebrovascular Reactivity (CVR) Assessed with Functional Near InfraRed Spectroscopy (fNIRS) as a Biomarker of Traumatic MicroVascular Injury (TVI) Measured Longitudinally after Acute TBI in Military Personnel  
Time Commitment: 3.0 calendar months  
Supporting Agency: MCNCoE, USUHS  
Level of Funding: \$200,000  
Performance Period: 10/1/2015 – 9/30/2017

Title: Targeted Alteration of Dietary Omega-3 and Omega-6 Fatty Acids for the Treatment of Post-Traumatic Headaches

Time Commitment: 2.0 calendar months

Level of Funding: \$3,252,840

Performance Period: 6/1/2015 – 5/31/2016

Title: Endophenotypes of dementia after traumatic brain injury in retired military service members

(Diaz-Arrastia, Co-I, Kenney, Project-Inv)

Time Commitment: 3 calendar months

Supporting Agency: CDMRP, DoD

Performance Period: 9/1/12-2/28/14

Level of Funding: \$480,000

### **Dr. Kramer:**

Summary: Dr. Kramer had two new grants begin.

Title: Effects of Chronic Inflammation on Brain Structures and Function (Kramer PI)

Time Commitment: 1.8 calendar months

Supporting Agency: NIA

Performance Period: 4/15/15-1/31/20

Level of Funding: \$391,509

Title: Hillblom Network for the Prevention of Age-Associated Cognitive Decline

Time Commitment: 1.2 calendar months

Supporting Agency: The Larry L. Hillblom Foundation

Performance Period: 1/1/15-12/31/18

Level of Funding: \$270,000

- **What other organizations were involved as partners?**
  - Nothing to report

### **Special Reporting Requirements**

Nothing to report